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RESEARCH CORRESPONDENCE

Initial bridge to transplant experience with a bioprosthetic autoregulated artificial heart

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The Carmat total artificial heart (C-TAH) is an electro-hydraulically–actuated heart replacement device with biocompatible blood-contacting materials and sensor-based autoregulation. It intends to replace the native heart in patients suffering from end-stage biventricular heart failure. The device provides fully pulsatile blood flow, adapted to the patient's activities by autoregulation.[1] This report summarizes the initial experience with clinical heart transplants from C-TAH implantation within an ongoing European Multicenter Pivotal Study with the primary end-point of 180-day post-implant survival or survival to cardiac transplantation (ClinicalTrials.gov Identifier: NCT02962973). The study was approved by relevant Ethics Committees and Regulatory Authorities. All patients signed informed consent to participate in the trial.

A total of 7 potentially transplant-eligible patients with end-stage biventricular failure (all men, mean age = 52.4 ± 9.7 years, and body surface area = 2.06 ± 0.16 m^2) were enrolled in the study within 11 months (refer to Supplementary Table S1 available online at www.jhltonline.org). Literature-derived comprehensive inclusion criteria suggestive of a need for biventricular support are summarized in Supplementary Table S2 online. A total of 3 patients suffered from ischemic cardiomyopathy, and 4 patients had non-ischemic cardiomyopathy. A total of 1 patient was in Interagency Registry for Mechanically Assisted Circulatory Support Profile 2, whereas all the remaining patients were in Interagency Registry for Mechanically Assisted Circulatory Support Profile 3. None of the patients had a previous sternotomy.

Consecutive candidates were subject to the virtual 3-dimensional computed tomography fit to ascertain anatomic compatibility (9 of 12 patients screened were compatible, and additional 2 patients were excluded owing to clinical ineligibility). The C-TAH was implanted as described previously.[2] In summary, after the establishing cardiopulmonary bypass aorta and pulmonary arteries are transected, both ventricles are removed, whereas both atria together with their atrioventricular junctions are preserved. Left atrial appendage exclusion is mandated. Atrial-connecting rings are attached and embraced within a metallic double-orifice–connecting device onto which the prosthesis is affixed (Figure 1). The pulmonary and aortic conduits are sutured to their respective arteries, and the device operation is commenced after deairing. Preventive measures to facilitate transplant re-entry by wrapping the right atrium and great arteries to prosthetic grafts conduits by expanded polytetrafluorethylene were performed almost uniformly. In addition, partial pericardial sac closure to optimize the prosthesis positioning was pursued in 1 patient. As a standard of care, definitive sternal closure on the following day only was entertained given the expected coagulopathy in patients with biventricular end-stage heart failure. A total of 3 patients exhibited peri-operative bleeding at the outflow conduit—device body interface—that was addressed by applying surgical glue. In 2 cases, post-operative re-exploration was needed immediately after implantation, and in 1 case, it was needed at 13 days after implantation (tamponade).

Despite comprehensive hemodynamic management, 3 patients required subsequent renal replacement therapy. A total of 2 of these patients remained dependent on chronic renal replacement therapy and developed multiorgan failure with systemic infection and hepatic dysfunction, leading to support withdrawal and death after 14 and 75 days, respectively (see Supplementary Table S3 online).

None of the 7 patients experienced any hemocompatibility-related adverse events such as pump thrombosis, hemolysis, stroke, or gastrointestinal bleeding (see Supplementary Table S3 online). A total of 5 patients progressed to intensive care discharge after a median of 7 days (range: 4−11 days) and were discharged from hospital at a median of 48 days (range: 36−68 days). Initially, the anticoagulation was managed with unfractionated heparin and further transitioned to enoxaparin (typical doses between 5,000 and 8,000 IU/day; target anti-Xa of 0.4 IU/ml) along with aspirin 100 mg/day. Once discharged, enoxaparin and aspirin were maintained, and patients remained predominantly outpatient, of whom, 2 were completely free from readmission (see Supplementary Table S4 online).

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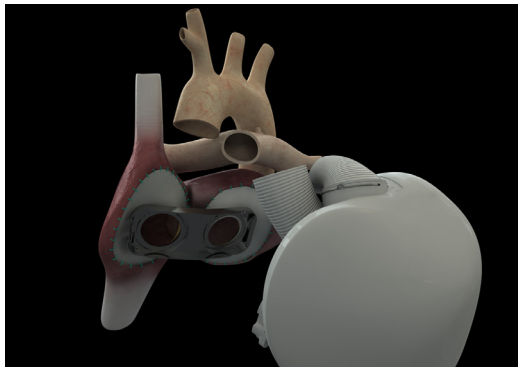

Figure 1 The Carmat prosthesis is snapped onto a titanium interface.

A total of 5 discharged patients recovered physiologic arterial blood pressure, cardiac output, renal and hepatic parameters, as well as hemoglobin levels. Functional capacity measured by 6-minute walk test and quality of life also improved over time (Table 1). Percutaneous driveline exit site infection was completely absent in all the survivors till transplantation.

Despite biologic materials blood flow path, there was no evidence of relevant human leukocyte antigen antibodies development in a longitudinal follow-up on support (see Supplementary Figure S1 online).

A total of 2 patients exhibited pulmonary arterial resistance (>6 Woods units), contraindicating direct transplantation listing. The implanted C-TAH precludes right heart catheterization. As an alternative, data from pressure sensors located inside the device were used to estimate a transpulmonary pressure gradient as an aid to longitudinally assess patients for transplant eligibility.

All the 5 discharged patients received donor hearts after a median support time period of 243 days (range: 109−308 days) in predominantly outpatient follow-up (see Supplementary Table S4 online). At transplantation, cardiopulmonary bypass was established mostly through femoral cannulation. Careful dissection was performed. Aorta and pulmonary artery were excised above the Dacron conduits, and percutaneous driveline was transected. The C-TAH was detached from the atrial interface. Adhesions around the body of the device were virtually absent in all patients. The atria were trimmed below their anastomoses with the device interface plate to allow for a routine bicaval technique in 2 cases and biatrial in 3 cases. Subsequently, the transplant procedure was completed in standard fashion, with induction therapy used in all cases.

All the 5 patients who had undergone transplantation were successfully discharged after transplantation, with 80% survival at 12 months because 1 patient developed pneumonia followed by a debilitating ischemic stroke 10 weeks after the transplantation and expired on Day 110 (Figure 2).

We believe that the study's key inclusion criteria were well indicative of biventricular circulatory support. More so, additional predictors of the high risk of right ventricular failure after isolated left ventricular assist device implantation advocated for selected strategy,[3] for example, considerably low pulmonary pulsatility index well descriptive of a ventricular−pulmonary uncoupling degree. Heart transplant candidates with such profiles represent an extremely challenging subset of patients with incompletely described natural fate on a waiting list. The question arises whether such fragile patients with comorbidities related to biventricular failure should be kept listed or more proactively treated with durable biventricular support or total artificial heart before deterioration. Indeed, despite technological progress, survival outcomes with durable dual left ventricular assist devices to the transplant are not yet ideal,[4] although limited data suggest a trend that simultaneous biventricular implantation may attain benefit over staged approach.[5]

The initial C-TAH experience documents the combination of encouraging hemocompatibility profile on C-TAH support along with physiologic fully pulsatile blood flow reflected by near normal laboratory values allowed for the optimal condition while patients await transplantation (Table 1). In addition, low intensity of anti-coagulation may reduce the risk of bleeding during the explant procedure.

Table 1 Laboratory Data, Hemodynamics, and Functional Status at Baseline (Before the Implant), Discharge, and Before Transplantation ($n = 5$)

Parameter	Baseline	At discharge	Before transplantation
Hemoglobin (g/dl)	13.6 ± 1.5	8.7 ± 0.8	11.6 ± 1.3
Creatinine (mg/dl)	1.1 ± 0.2	0.8 ± 0.2	0.9 ± 0.1
Sodium (mmol/liter)	134.0 ± 5.5	136.1 ± 4.8	139.5 ± 4.0
Total bilirubin (mg/dl)	0.88 ± 0.53	0.49 ± 0.07	0.68 ± 0.09
Albumin (g/dl)	4.1 ± 0.4	3.4 ± 0.4	4.4 ± 0.2
Lactate dehydrogenase (U/liter)	207.3 ± 49.6	226.8 ± 54.0	223.1 ± 52.5
Plasma free hemoglobin (mg/dl)	6.3 ± 2.7	3.0	3.0 ± 1.2
Cardiac index (liter/min/m^2)	1.6 ± 0.4	3.0 ± 0.2	2.8 ± 0.2
Systolic blood pressure (mm Hg)	101.0 ± 10.3	119.0 ± 12.5	120.0 ± 14.1
Diastolic blood pressure (mm Hg)	69.4 ± 4.0	78.0 ± 8.4	76.0 ± 5.5
EQ5D–VAS score	40.0 ± 21.6	73.8 ± 12.5	70.0 ± 15.8
6-minute walk distance (m)	144.0 ± 135.4	251.3 ± 68.6	315.0 ± 60.5

Abbreviations: VAS, visual analog scale.
Values are displayed as mean with SD.

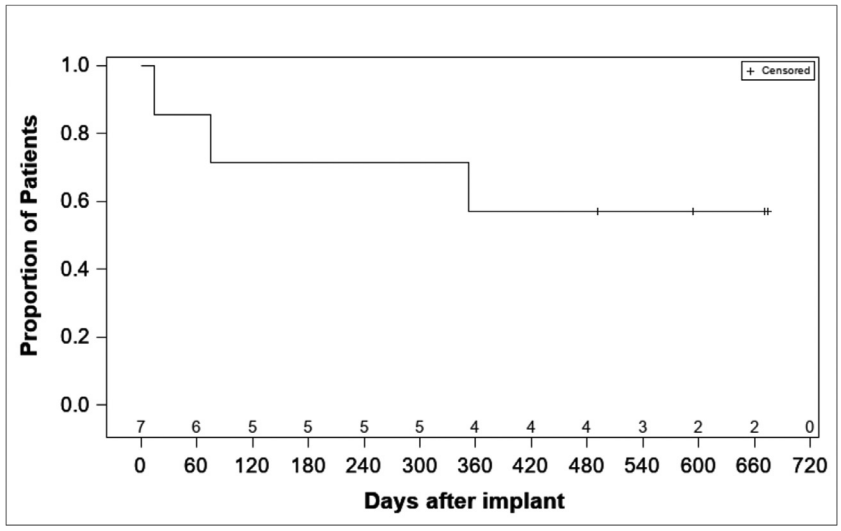

Figure 2 Post-implant survival (Kaplan−Meier analysis) censored at the latest follow-up time point.

In our limited experience, there were no tissue adhesions around the prosthesis. This might be attributed to the smooth polyurethane sac that surrounds the device acting as a compliance chamber with miniature motion excursions, preventing adhesion formation. Another potential advantage of the C-TAH is that its shape and size resemble those of a natural heart and thus preserves sufficient space for the transplanted donor heart. Pericardial space shrinking constituted a limitation with existing total artificial hearts and, particularly, dual continuous flow pumps and mandated alternative mitigation strategies.

In summary, early observations suggest that a successful bridging to heart transplantation with the C-TAH is feasible. However, further experience accrual is warranted to better define the potential benefits of such therapy.

Disclosure statement

Dr Netuka reports receiving grants and non-financial support from Carmat SA during the conduct of the study; grants, personal fees, and non-financial support from Carmat SA and Abbott; non-financial support and other fees from LeviticusCardio Ltd.; and personal fees and non-financial support from Evaheart Inc., outside the submitted work. Dr Ivak reports receiving grants, personal fees, and non-financial support from Carmat SA during the conduct of the study; and personal fees and non-financial support from Carmat SA and grants, personal fees, and non-financial support from Abbott outside the submitted work. Dr Konarik reports receiving grants, personal fees, and non-financial support from Carmat SA during the conduct of the study; and non-financial support from Carmat SA outside the submitted work. Dr Gustafsson reports receiving personal fees from Carmat SA and Abbott during the conduct of the study; grants, personal fees, and non-financial support from Pfizer, Boehringer-Ingelheim, Bayer, Orion Pharma, AstraZeneca, and Novartis; and non-financial support from Corvia Medical outside the submitted work. Dr Smadja reports receiving personal fees and others from Carmat SA during the conduct of the study; person fees from Aspen and Léo Pharma and other fees from Boerhinger outside the submitted work. Dr Jansen reports receiving fees other from Carmat SA during the conduct of the study. Dr Latrémouille reports to be a Carmat consultant during the conduct of the study. The remaining authors have no conflicts of interest to disclose.

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Supplementary materials

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Supplementary data

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